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Sleep duration, insomnia, and markers of systemic inflammation: Results from the Netherlands Study of Depression and Anxiety (NESDA)

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ABSTRACT

Systemic inflammation has emerged as a potential pathway linking depressive and anxiety disorders with disease risk. Short and long sleep duration, as well as insomnia, are common among psychiatric populations and have previously been related to increased inflammation. The aim of the present study was to investigate associations between sleep duration and insomnia with biomarkers of inflammation and to explore whether these associations varied by psychiatric diagnostic status. To this end, self-reported measures of sleep duration, insomnia symptoms, and markers of inflammation, including C-reactive protein (CRP), interleukin-(IL)-6, and tumor necrosis factor (TNF)-α, were obtained in 2553 adults (aged 18–65 years) diagnosed with current/recent or remitted depressive and/or anxiety disorders and healthy controls enrolled in the Netherlands Study of Depression and Anxiety (NESDA). Regression analyses revealed associations between sleep duration and levels of CRP and IL-6 with higher levels observed in long sleepers. These associations remained statistically significant after controlling for age, gender, education, body mass index, smoking, alcohol consumption, medical comorbidities, medication use, psychotropic medication use, and psychiatric diagnostic status. There were no clear associations between insomnia symptoms and levels of inflammation. Relationships between sleep duration and inflammation did not vary as a function of psychiatric diagnostic status. These findings suggest that elevated levels of systemic inflammation may represent a mechanism linking long sleep duration and disease risk among those with and without depressive and anxiety disorders.

1. Introduction

Depression and anxiety disorders are highly prevalent and co-morbid psychiatric disorders with substantial consequences for physical health, including increased incidence and progression of a number of age-related diseases such as cardiovascular disease, diabetes, and the metabolic syndrome (Eaton et al., 1996; Lett et al., 2004; Raikkonen et al., 2007; Suls and Bunde, 2005). The biological mechanisms linking these psychiatric conditions to physical health remain unclear; however, low-grade chronic inflammation has emerged as a key biological pathway.

Several meta-analytic reviews support elevations in inflammatory markers, such as pro-inflammatory cytokines interleukin (IL)-6, tumor necrosis factor (TNF)-α, and acute phase proteins, such as C-reactive protein (CRP), in depressed compared to non-depressed patients (Dowlati et al., 2010; Howren et al., 2009; Zorrilla et al., 2001). Elevations are also observed in those with clinical anxiety (O'Donovan et al., 2010; Vogelzangs et al., 2013); however, this link is less well characterized (O'Donovan et al., 2013). Not all studies have been consistent, however, which may reflect the heterogeneity that exists within the diagnostic categories of Depressive and Anxiety Disorders (Goldberg, 2011; Insel and Wang, 2010). Accordingly, researchers have begun to focus attention on symptoms relevant across psychiatric conditions (i.e., transdiagnostic processes); sleep disturbance has emerged as one such symptom (Harvey et al., 2011).

Growing evidence suggests that disturbed sleep is associated with elevations in systemic levels of inflammation. For instance, in

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several though not all laboratory studies (reviewed in Solarz et al. (2012)) healthy sleepers subjected to total and partial sleep restriction show significant elevations in inflammatory activity compared to an undisturbed sleep condition (Irwin et al., 2006; Shearer et al., 2001; Vgontzas et al., 1999, 2004). Further, compared to nondepressed controls, depressed patients displayed higher nocturnal levels of IL-6, a difference that is partially accounted for by a longer time to sleep onset in the depressed patients (Motivala et al., 2005). Whether these associations extend beyond the laboratory setting remains unclear. In this regard, greater inflammation has been documented in patients with insomnia compared to non-disturbed sleepers (Burgos et al., 2006). Further, short (e.g., sleeping less than 5 or 6 h per night) and/or long sleep duration (e.g., sleeping more than 9 or 10 h per night) have been associated with higher levels of inflammation compared to those reporting typical sleep duration (i.e., 7–8 h per night) in several large epidemiologic investigations (Dowd et al., 2011; Miller et al., 2009). While curvilinear associations are not supported in all studies, these findings map onto prevalence rates of several chronic diseases and early mortality observed at higher frequency among short and long sleepers (Ayas et al., 2003a, 2003b; Cappuccio et al., 2010a, 2010b; Hall et al., 2008; Heslop et al., 2002). For instance, Hall et al. found that compared to normal sleepers (7–8 h) both short (<6 h per night) and long (>8 h) showed significantly increased odds of meeting diagnostic criteria for the metabolic syndrome, independent of other sociodemographic characteristics and health behaviors (Hall et al., 2008).

Despite converging evidence for a link between psychopathology, namely depression and to some extent anxiety, sleep, and markers of inflammation, no study has sought to systematically examine their inter-relationships in a large sample. The goals of the present study are to 1) estimate the associations between poor sleep, as characterized by short and/or long sleep duration and insomnia symptoms, with markers of systemic levels of inflammation (CRP, IL-6, and TNF-α) in a large sample of patients with current and past psychopathology (depressive and/or anxiety disorder) and never diagnosed controls and 2) determine whether psychopathology status moderates the sleep-inflammation link. The proposed study utilizes data from the Netherlands Study of Depression and Anxiety (NESDA) which have previously demonstrated differential elevations in markers of inflammation in patients with psychopathology compared to healthy controls (Vogelzangs et al., 2013; Vogelzangs et al., 2012). Given that sleep is a modifiable health behavior, understanding the extent to which sleep drives inflammatory activity in the context of psychopathology may have important implications for treatment.

2. Methods

2.1. Study sample

The Netherlands Study of Depression and Anxiety (NESDA) is an ongoing cohort study designed to investigate the long-term course and consequences of depressive and anxiety disorders. Participants were adults aged 18–65 recruited from community (19%), general practice (54%), and secondary mental health (27%) facilities. A total of 2981 participants, including persons with current/recent or past depressive and/or anxiety disorders and healthy controls, were assessed at baseline between 2004 and 2007. Exclusion criteria for the NESDA study were not speaking the Dutch language and a known clinical diagnosis of bipolar disorder, obsessive–compulsive disorder, severe addiction disorder, psychotic disorder or organic psychiatric disorder.

A detailed description of the NESDA study design can be found elsewhere (Penninx et al., 2008). Briefly, the baseline assessment was comprised of a face-to-face interview, including a standardized diagnostic psychiatric interview, a medical assessment, computer tasks, written questionnaires, and biological measurement (among which was a blood draw in a fasting state). The research protocol was approved by the Ethical Committee of participating universities and after complete description of the study all respondents provided written informed consent.

Of the final 2981 participants included in the baseline assessment of NESDA, 428 had missing data concerning sleep duration ($n = 358$) or inflammation ($n = 70$) and were excluded from the current study, resulting in a sample size of 2553 participants. An additional 4 participants were missing data on the Insomnia Rating Scale (IRS) yielding 2549 participants in analyses that include IRS data.

Compared to those included in the present analysis, excluded participants were significantly younger ($t(2979) = -6.08$, $p < 0.001$), more likely to be male ($X^2(1) = 5.99$, $p = 0.01$), less educated ($t(2979) = -6.57$, $p < 0.001$), more likely to be a current smoker ($X^2(2) = 55.23$, $p < 0.001$), to use benzodiazepines ($X^2(1) = 6.46$, $p = 0.01$), less likely to be on anti-inflammatory medication ($X^2(1) = 4.91$, $p = 0.03$), less likely to be free from antidepressant medication ($X^2(3) = 12.59$, $p < 0.001$) and more likely to be diagnosed with comorbid current/recent depressive and anxiety disorders ($X^2(4) = 46.07$, $p < 0.001$).

2.2. Measures

2.2.1. Sleep duration and insomnia

Measures of sleep duration and insomnia were obtained as part of a questionnaire that participants completed after the interview or at home. Sleep duration was obtained by asking participants' "How many hours per night did you sleep on average during the last 4 weeks?" Answer options were: "10 or more hours", "9 h", "8 h", "7 h", "6 h", "5 or less h." In descriptive analyses, sleep duration scores were used to categorize participants as short sleepers (≤6 h per night), normal sleepers (7–9 h per night), and long sleepers (≥10 h per night); however, in the primary regression analyses, sleep duration was treated as a continuous variable.

Insomnia was assessed using the Women's Health Initiative Insomnia Rating Scale (IRS) (Levine et al., 2003a). This scale consists of five questions that address trouble falling asleep, waking up during the night, early morning awakenings, trouble getting back to sleep after waking up, and sleep quality in the past month. The total score for this scale ranges from 0 (no insomnia) to 20 (severe insomnia). The IRS has good test-retest reliability and is strongly associated with other actigraphy-related sleep measures (Levine et al., 2003b). The IRS showed good internal validity in this sample (Cronbach $\alpha = 0.83$). Scores on the IRS were dichotomized at the cut-off point of 9 for descriptive analyses. This cut point has shown to indicate clinically significant insomnia (Levine et al., 2003a); however, in primary regression analyses, scores on the IRS were treated as a continuous variable.

2.2.2. Psychopathology

The presence of psychiatric disorders was determined by using the Composite International Diagnostic Interview (CIDI, versions 2.1). The CIDI is a standardized psychiatric diagnostic interview that follows the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria to establish diagnoses. The CIDI is a highly reliable and valid instrument for assessing depressive and anxiety disorders (Wittchen, 1994) and was administered by specially trained research staff. Depressive disorder (major depressive disorder, dysthymia) status was categorized as follows: current/recent diagnosis (i.e., past 6 months), remitted (i.e., lifetime diagnosis but not in the past 6 months), controls (no lifetime

diagnosis). Assessed anxiety disorders included panic disorder, agoraphobia, generalized anxiety disorder, and social phobia and were categorized similarly as current/recent diagnosis, remitted diagnosis, or controls. Based on the above diagnostic categories, participants were categorized as follows: never diagnosed ($n = 593$), remitted ($n = 556$), current/recent depressive disorder ($n = 334$), current/recent anxiety disorder ($n = 467$), comorbid current/recent depressive and anxiety disorders ($n = 603$).

2.2.3. Inflammatory markers

Fasting blood samples were obtained at the baseline NESDA measurement to assess markers of systemic inflammation, including CRP, IL-6, and TNF-α. Samples were obtained in the morning between 8 and 9 am and kept frozen at −80 °C until assay. CRP and IL-6 were assayed at the Clinical Chemistry department of the VU University Medical Center. High-sensitivity plasma levels of CRP were measured in duplicate by an in-house enzyme-linked immunosorbent assay (ELISA) based on purified protein and polyclonal anti-CRP antibodies (Dako, Glostrup, Denmark). Intra- and inter-assay coefficients of variation were 5% and 10%, respectively. Plasma IL-6 levels were measured in duplicate by high sensitivity ELISA (PeliKine Compact ELISA, Sanquin, Amsterdam, The Netherlands). Intra- and inter-assay coefficients of variation were 8% and 12%, respectively. Plasma TNF-α levels were assayed in duplicate at Good Biomarker Science, Leiden, The Netherlands, using high-sensitivity solid phase ELISA (Quantikine HS Human TNF-α Immunoassay, R&D Systems, Minneapolis, MN, United States). Intra- and inter-assay coefficients of variation were 10% and 15%, respectively.

2.2.4. Study covariates

2.2.4.1. Sociodemographic characteristics. Sociodemographic factors previously found to be associated with sleep, depression and anxiety, and inflammatory activity included age (in years), gender, and education (in years).

2.2.4.2. Health indicators. A number of health factors were assessed including body mass index (weight in kilograms divided by height in meters squared), self-reported smoking status (never, former, current), alcohol intake categorized by the number of alcoholic drinks per week as none (less than 1 per week), moderate (for males, 1–21 drinks per week; for females, 1–14 drinks per week), and heavy (for males, >21 drinks per week; for females, >14 drinks per week), and physical activity (measured with the International Physical Activity Questionnaire (Craig et al., 2003)) in MET-minutes (ratio of energy expenditure during activity compared to a reference metabolic rate) per week). In addition, several diseases were taken into account, including presence of cardiovascular disease (assessed by self-report supported by appropriate medication use (Vogelzangs et al., 2010), presence of diabetes (based on fasting plasma glucose level ≥7.0 mmol/l or use of anti-diabetic medication), and number of self-reported chronic diseases for which persons received treatment (including lung disease, osteoarthritis, cancer, ulcer, intestinal problems, liver disease, and thyroid gland disease). Medication use was also assessed based on drug container inspection of all drugs used in the past month and classified according to the World Health Organization Anatomical Therapeutic Chemical classification and included use of statins (C10AA, C10B) and any systemic anti-inflammatory medication (M01A, M01B, A07EB and A07EC).

2.2.4.3. Psychotropic medication. These medications were only considered when taken on a regular basis and included benzodiazepines (N05BA, N05CF, N05CD, and N03AE), selective serotonin re-uptake inhibitors (SSRIs; N06AB), serotonin-norepinephrine reuptake inhibitors (SNRI; N06AX16 and N06AX21) (e.g., venlafaxine), tricyclic antidepressants (TCA; N06AA), and tetracyclic antidepressants (TeCA), including mirtazapine and trazodone (N06AX03, N06AX05, and N06AX11).

2.3. Statistical analyses

The goals of this study were to examine the cross-sectional associations between sleep duration and insomnia symptoms with measures of systemic inflammation (CRP, IL-6, TNF-α) and whether these associations varied by psychiatric diagnostic status. Data were analyzed using SPSS 22.0 (SPSS Inc., Chicago, Illinois).

Pearson product–moment correlations, independent *t*-tests, Analysis of Variance (ANOVA) including post-hoc comparisons, and chi-squared tests were employed to examine associations between study covariates with measures of sleep and levels of systemic inflammation. To examine associations between sleep measures and levels of systemic inflammation multiple linear regression analyses were computed adjusting for sociodemographic characteristics (age, gender, education) and body mass index (BMI) in the first step, followed by the sleep measure of interest entered as a continuous variable in the next step of each model. To identify other covariates to include in subsequent models, bivariate associations between possible covariates and markers of inflammation were first calculated. Factors that were significantly associated with at least one inflammatory marker were retained in subsequent models (Table 2). This strategy was pursued in order to conserve power and increase degrees of freedom in multivariate models. In this regard, multivariate regression models were adjusted for sociodemographic factors and BMI with additional covariates entered stepwise in blocks as follows: health indicators (smoking status, alcohol use, presence of cardiovascular disease, presence of diabetes, number of chronic medical conditions, statin use, and anti-inflammatory medication use); psychotropic medication (benzodiazepine and anti-depressant use) and psychiatric diagnostic status (never diagnosed, remitted, current depressive disorders, current anxiety disorders, and current depressive and anxiety disorders).

Based on literature demonstrating linear and nonlinear effects of sleep duration on biomarkers (Dowd et al., 2011; Patel et al., 2009) sleep duration was modeled as a linear and nonlinear predictor (i.e., sleep duration squared term) in separate models. In models where the nonlinear sleep duration measure was treated as the predictor, sleep duration as a linear term was included as an additional covariate.

Because several regression models supported nonlinear associations between sleep duration and measures of inflammation, follow up analyses of differences in levels of inflammation across sleep duration categories were estimated using Analysis of Covariance (ANCOVA). Here, sleep duration values were categorized into ≤6 h (short sleep duration), 7–9 h (normal sleep duration), and ≥10 h (long sleep duration). Cohen's *d*s were calculated to provide estimates of effect size.

Finally, to test whether associations between measures of sleep and inflammation differed by psychiatric diagnostic status, we tested for interactions by including sleep duration*psychiatric diagnostic status, sleep duration (squared term)*psychiatric status, and insomnia scores*psychiatric diagnostic status interaction terms in separate multiple linear regressions adjusting for age, gender, education, and BMI. To conserve power for these analyses, sleep duration and insomnia scores were treated as continuous predictors. Stratified models were pursued only if supported by statistically significant interactions. Distributions of CRP, IL-6, and TNF-α were non-normally distributed and underwent natural log transformation to better approximate a normal distribution.

Table 1
Baseline characteristics stratified by sleep duration and insomnia status.

	Sleep duration (h)				Insomnia status		
	≤6 h ($n = 718$)	7–9 h ($n = 1731$)	10 h ≥ ($n = 104$)	p-value	IRS < 9 ($n = 1436$)	IRS ≥ 9 ($n = 1113$)	p-value
Gender (% female)	63.0	68.2	81.7	<0.001	66.6	68.1	0.414
Age (yrs)	46.9 (11.4)	40.9 (13.2)	37.3 (13.4)	<0.001	40.5 (13.2)	45.0 (12.4)	<0.001
Education (yrs)	11.5 (3.3)	12.7 (3.2)	11.7 (3.3)	<0.001	12.6 (3.2)	12.0 (3.3)	<0.001
Smoking status				0.002			0.262
Never, %	24.9	30.8	28.8		30.2	27.6	
Former, %	34.6	35.2	24.0		33.9	36.5	
Current, %	38.7	34.0	47.1		35.9	35.9	
Alcohol intake				0.004			<0.001
<1 drinks/week, %	35.4	29.8	40.8		30.3	33.8	
1–14 (women); 1–21 drinks/week (men), %	51.9	59.4	48.5		60.1	52.4	
>14 (women); >21 (men) drinks/week, %	12.7	10.8	10.7		9.6	13.8	
Physical activity (MET-min per week)	3974.2 (3582.9)	3601.0 (2861.9)	2856.7 (3212.8)	<0.001	3721.0 (3016.4)	3623.6 (3212.9)	0.449
Body Mass Index (kg/m^2)	26.6 (5.2)	25.1 (4.6)	25.6 (6.1)	<0.001	25.2 (4.8)	25.9 (5.0)	<0.001
Cardiovascular disease, %	9.7	4.1	7.8	<0.001	4.8	7.1	0.011
Diabetes, %	7.8	3.7	4.9	<0.001	4.3	5.6	0.145
Number of medical conditions	0.8 (1.0)	0.5 (0.8)	0.9 (1.1)	<0.001	0.5 (0.8)	0.8 (1.0)	<0.001
Medication use							
Statins, %	11.2	5.1	8.7	<0.001	5.9	8.4	0.014
Anti-inflammatory, %	6.9	3.8	4.9	0.006	3.4	6.5	<0.001
Antidepressant use				<0.001			<0.001
None, %	75.2	78.1	50.5		80.1	71.1	
SSRI, %	15.7	15.1	40.8		14.3	19.0	
SNRI, %	4.2	3.5	1.9		2.7	4.9	
TCA, %	2.8	2.1	4.9		1.8	3.1	
TeCA, %	2.1	1.2	1.9		1.1	1.9	
Benzodiazepines, %	12.6	4.9	8.7	<0.001	3.4	12.1	<0.001
Diagnostic status				<0.001			<0.001
Never diagnosed, %	13.2	28.1	10.6		32.6	11.1	
Remitted, %	21.0	22.9	7.7		25.0	17.6	
Current depressive disorder, %	14.8	12.0	19.2		10.2	16.8	
Current anxiety disorder, %	15.3	19.9	11.5		18.1	18.5	
Current depressive and anxiety disorder, %	35.7	17.0	51.0		14.1	36.0	

3. Results

3.1. Descriptive statistics

Baseline characteristics of the present sample grouped by sleep duration category and insomnia status are presented in Table 1. Consistent with previously published findings (van Mill et al., 2010), short sleepers (i.e., sleeping ≤ 6 h per night) were more likely to be men, older, less educated, heavier, current smokers, consume fewer than 1 alcoholic drink per week, have diabetes, cardiovascular disease and a greater number of medical conditions, use statins, anti-inflammatory medications and benzodiazepines, and to have a current psychiatric diagnosis, particularly comorbid depressive and anxiety disorders compared to normal sleepers (i.e., participants sleeping 7–9 h per night). Long sleepers (i.e., sleeping ≥ 10 h per night), compared to normal sleepers, were more likely to be women, younger, less educated, be a current smoker, consume fewer than 1 drink per week, less physically active, a higher number of medical conditions, to use SSRI medication and have a current depressive or a comorbid depressive and anxiety disorder diagnosis.

Participants with insomnia (IRS ≥ 9), as compared to those without insomnia (IRS < 9), were older, less educated, heavier, more likely to be a heavy drinker of alcohol, have cardiovascular disease and more other medical conditions, more likely to take statins and anti-inflammatory medications, use antidepressants, use benzodiazepines, and to be diagnosed with depressive disorders or comorbid depressive and anxiety disorders.

Associations between inflammatory markers and study covariates, including sociodemographic characteristics, health indicators, and psychotropic medication use are provided in Table 2. Analyses revealed that participants with higher levels of inflammation were older, more likely to be men, less educated, more likely to be current smokers, reported no alcohol consumption or heavy alcohol consumption, reported more chronic diseases, were more likely to have cardiovascular disease and diabetes, and more likely to use benzodiazepines and antidepressants. Pearson correlations revealed that levels of inflammatory markers were low to modest but significantly inter-correlated (p's < 0.001) (CRP-IL-6, $r = 0.31$; CRP-TNF-α: $r = 0.12$; IL-6-TNF-α: $r = 0.12$).

3.2. Sleep and levels of systemic inflammation

As displayed in Table 3, regression models treating self-reported sleep duration as either a linear or nonlinear term and adjusting for age, gender, education, and BMI, revealed statistically significant associations with levels of CRP and IL-6 but not TNF-α. Longer sleep duration continued to be significantly associated with linear increases in levels of CRP after adjusting for additional covariates including health indicators (smoking status, alcohol consumption, presence of CVD and diabetes, number of chronic diseases), medication use (statins, anti-inflammatory medication, psychotropic medications), and psychiatric diagnostic status. Conversely, sleep duration, modeled as a nonlinear predictor, was significantly associated with levels of IL-6, which suggests that long and short sleep duration is related to higher levels of IL-6. Scores on the

Table 2
Associations between study covariates and markers of systemic inflammation.

	CRP[a]	IL-6[a]	TNF-α[a]
Age (years)	0.09**	0.16**	0.07**
Gender			
Men	1.10 (1.04)	0.80 (1.03)*	0.85 (1.02)
Women	1.34 (1.03)**	0.74 (1.02)	0.82 (1.02)
Education (years)	−0.17**	−0.12**	−0.08**
Body Mass Index (kg/m^2)	0.42**	0.26**	0.11**
Smoking Status[b]			
Never	1.13 (1.05)	0.70 (1.04)	0.85 (1.02)
Former	1.22 (1.04)	0.73 (1.03)	0.83 (1.02)
Current	1.43 (1.04)**	0.84 (1.03)*	0.83 (1.02)
Alcohol consumption[c]			
None	1.54 (1.05)**	0.85 (1.05)**	0.89 (1.02)**
Moderate	1.12 (1.03)	0.70 (1.03)	0.80 (1.02)
Heavy	1.30 (1.07)	0.82 (1.05)*	0.81 (1.03)
Physical activity (METs/week)	−0.04	−0.02	0.01
Presence of CVD			
Yes	1.73 (1.10)**	1.01 (1.06)**	1.00 (1.05)**
No	1.23 (1.03)	0.75 (1.02)	0.82 (1.01)
Presence of diabetes			
Yes	1.99 (1.10)**	1.13 (1.08)**	0.98 (1.06)*
No	1.23 (1.03)	0.74 (1.02)	0.82 (1.01)
# of chronic diseases	0.11**	0.14**	0.10**
Statin use			
Yes	1.51 (1.09)**	1.02 (1.06)*	0.98 (1.04)**
No	1.24 (1.03)	0.74 (1.02)	0.82 (1.01)
Anti-inflammatory use			
Yes	1.89 (1.12)**	0.97 (1.11)*	0.86 (1.05)
No	1.23 (1.03)	0.75 (1.02)	0.83 (1.02)
Benzodiazepine use			
Yes	1.59 (1.09)*	0.95 (1.06)*	0.89 (1.05)
No	1.24 (1.03)	0.75 (1.02)	0.82 (1.01)
Antidepressant use[d]			
None	1.18 (1.03)	0.73 (1.02)	0.83 (1.01)
SSRI	1.40 (1.07)*	0.85 (1.04)*	0.82 (1.03)
SNRI	1.37 (1.14)	0.93 (1.12)*	0.79 (1.05)
TCA	2.43 (1.18)**	0.91 (1.12)	1.04 (1.08)*
Tetracyclic	2.48 (1.24)**	1.05 (1.20)*	0.82 (1.09)
Psychiatric status[e]			
Never diagnosed	1.14 (1.05)	0.73 (1.04)	0.83 (1.03)
Remitted	1.22 (1.05)	0.69 (1.04)	0.83 (1.03)
Current/Recent depressive disorder	1.30 (1.07)	0.78 (1.05)	0.84 (1.03)
Current/Recent anxiety disorder	1.30 (1.06)	0.79 (1.05)	0.80 (1.03)
Current/Recent comorbid depressive & anxiety disorders	1.37 (1.05)	0.80 (1.04)*	0.86 (1.03)

*$p < 0.05$; **$p < 0.001$.
[a] To normalize distributions CRP, IL-6, and TNF-α values were natural log transformed; for interpretation purposes means are presented as back transformed.
[b] Post hoc comparisons vs. never smoked.
[c] Post hoc comparisons vs. moderate alcohol consumption.
[d] Post hoc comparisons vs. no antidepressant use.
[e] Post hoc comparisons vs. never diagnosed.

Insomnia Rating Scale were not statistically significantly related to levels of any of the inflammatory markers in this sample.

To better characterize the associations between sleep duration and inflammation, sleep categories (≤6 h (short sleep duration), 7–9 h (normal sleep duration), and ≥10 h (long sleep duration)) were derived (van Mill et al., 2010) (Table 4). Compared to normal sleepers, participants sleeping 10 or more hours per night displayed statistically significantly higher levels of IL-6 and CRP,[1] and these associations remained significant after adjustment for sociodemographic characteristics, health indicators, and psychotropic and psychiatric diagnostic status. Effect sizes (Cohen's *d*) for the difference in CRP and IL-6 between long sleepers and normal ranged from 0.240 to 0.392, indicating a small to medium effect. In contrast, levels of CRP and IL-6 were statistically similar between short and normal sleepers.

Relationships between sleep duration, modeled as linear and nonlinear predictors, and insomnia symptoms with markers of inflammation did not vary as a function of psychiatric diagnostic status (interaction *p*'s > 0.05). Accordingly, analyses within each psychiatric diagnostic group were not pursued.

4. Discussion

This study revealed significant associations between self-reported sleep duration and circulating levels of pro-inflammatory mediators in a large sample of participants with and without depressive and anxiety disorders. Specifically, we found that individuals reporting longer sleep duration, modeled as either a continuous or categorical predictor (≥10 h per night), displayed significantly higher levels of CRP and IL-6 and that these associations were independent of sociodemographic variables, health indicators, and psychiatric diagnostic status. These findings extend prior investigations in this well characterized sample (van Mill et al., 2010; Vogelzangs et al., 2013; Vogelzangs et al., 2012) and are consistent with several earlier epidemiologic studies (Dowd et al., 2011; Grandner et al., 2013; Patel et al., 2009; Williams et al., 2007). For example, in a large sample of Taiwanese participants, those reporting longer sleep duration displayed elevations in CRP and IL-6 and were more likely than normal sleepers to have CRP values greater than 3.0 mg/dL (Dowd et al., 2011).

The present study failed to find support for a link between short sleep duration or insomnia status with markers of inflammation. While this is consistent with other prior studies (Dowd et al., 2011; Grandner et al., 2013; Matthews et al., 2010; Patel et al., 2009; Taheri et al., 2007), it runs counter to laboratory based studies that observe elevated inflammatory activity in response to acute sleep restriction (Irwin et al., 2006; Shearer et al., 2001; Vgontzas et al., 2004). One potential explanation involves the fact that studies utilizing sleep restriction typically recruit and screen participants who are habitual 7–8 h sleepers who then experimentally have their sleep opportunity diminished. In contrast, self-reported short sleepers may sleep fewer hours for varied reasons (Horne, 2011). For instance, while some short sleepers may have a lower underlying sleep need, others may sleep less by necessity (e.g., employment responsibilities) and thus the latter may reflect a form of chronic sleep restriction.

The analyses did not support unique associations between sleep and inflammation among individuals with current/recent or past psychopathology relative to participants free of psychiatric conditions. While these findings suggest that longer sleep duration was associated with elevated levels of IL-6 and CRP irrespective of psychiatric diagnostic status, there are several caveats that should be considered. For instance, hypersomnia, which is characterized by excessive daytime sleepiness and prolonged sleep duration, was not explicitly assessed beyond self-reported sleep duration. Hypersomnia occurs in roughly 15% of patients with depression (reviewed in Franzen and Buysse (2008)) and possibly accounts for some of the variability in inflammation observed in depressed individuals (Dowlati et al., 2010). Longer sleep duration was a significant predictor of IL-6 and CRP, independent of psychiatric diagnostic status; however, because hypersomnia is itself a psychiatric condition that was not assessed in this study, the role of hypersomnia in explaining some of the relationship between long sleepers and inflammation cannot be ruled out. Accordingly, future work carefully characterizing hypersomnia, as well as other aspects of sleep complaints, is warranted. It is also notable that long

[1] Similar significant findings are observed when long sleepers, categorized as ≥9 h per night, are compared to 7–8 h sleepers (IL-6; $p = 0.014$; CRP; $p = 0.045$).

Table 3
Multiple linear regression models estimating associations between sleep measures and markers of inflammation.

	CRP[a]		IL-6[a]		TNF-α[a]	
	b (SE)	*p*-value	*b* (SE)	*p*-value	*b* (SE)	*p*-value
Sleep duration (linear)						
Model 1	0.043 (0.018)	0.020	0.029 (0.015)	0.061	0.005 (0.010)	0.598
Model 2	0.046 (0.018)	0.013	0.030 (0.015)	0.050	0.007 (0.010)	0.497
Model 3	0.041 (0.018)	0.026	0.028 (0.015)	0.067	0.007 (0.010)	0.518
Sleep duration (quadratic)[b]						
Model 1	0.024 (0.011)	0.037	0.033 (0.010)	0.001	0.010 (0.006)	0.107
Model 2	0.021 (0.012)	0.073	0.028 (0.010)	0.004	0.007 (0.006)	0.277
Model 3	0.018 (0.012)	0.134	0.026 (0.010)	0.009	0.008 (0.007)	0.241
Insomnia Rating Scale						
Model 1	0.000 (0.004)	0.951	−0.002 (0.004)	0.599	−0.002 (0.002)	0.467
Model 2	−0.001 (0.004)	0.826	−0.003 (0.004)	0.359	−0.003 (0.002)	0.270
Model 3	−0.002 (0.005)	0.733	−0.005 (0.004)	0.205	−0.003 (0.003)	0.292

Model 1: covariates include age, gender, education, and body mass index; Model 2: includes additional adjustments for smoking status, alcohol use, presence of cardiovascular disease and diabetes, number of chronic medical conditions, statin use, and anti-inflammatory medication use; Model 3 includes additional adjustments for psychotropic medication use and psychiatric diagnostic status.
[a] Natural log transformed.
[b] Sleep duration as a linear term was included as a covariate in all models.

sleepers (i.e., ≥10 h per night) comprised only 4% of the sample. The analytic strategy pursued in the present study treated the sleep duration variable as a continuous predictor, thus utilizing the full sample (n = 2553) and providing adequate power to test interactions. Nevertheless, a larger sample of long sleepers may have improved our ability to detect small differences between psychiatric diagnostic groups.

The mechanisms linking long sleep and inflammation remain to be fully elucidated. In this regard, long sleep may reflect unmeasured or subclinical processes where inflammation plays a pathogenic role, such as in infectious illness or autoimmune conditions. While this study statistically adjusted for several important medical comorbidities, including cardiovascular disease and diabetes among others, unaccounted medical conditions may have played a contributory role in the sleep-inflammation link. The cross-sectional nature of this data cannot rule out the possibility that inflammation contributes to long sleep. Indeed, experimental animal and human studies support the soporific effects of proinflammatory mediators (Bryant et al., 2004). Further, six-year increases in inflammation have been shown to predict the likelihood of being categorized as a long sleeper at year 6 in a large sample (Dowd et al., 2011). Finally, circadian factors may also play a role. For instance, longer sleepers have been found to have a longer duration of melatonin secretion, a hormone critical to sleep promotion in humans. In vitro studies suggest that the relationship between melatonin and inflammation is complex (Carrillo-Vico et al., 2013), including the capacity for melatonin to activate monocytes (Morrey et al., 1994), a primary cellular source of inflammation, and enhance proinflammatory cytokine production in cultured cells (Garcia-Maurino et al., 1997).

The fact that both IL-6 and CRP were higher among longer sleepers in this sample is in line with prospective evidence linking long sleep duration to increased risk for all-cause mortality and negative cardiovascular outcomes (Youngstedt and Jean-Louis, 2011; Youngstedt and Kripke, 2004). As such, this raises questions about whether long sleepers should be targets for intervention. In this regard, trials employing chronic moderate sleep restriction in long sleepers are currently underway, and results will likely aid in understanding the long sleep-inflammation link (Youngstedt et al., 2013). Better characterization of long sleepers, including psychological, behavioral, and neurobiological correlates, may also illuminate opportunities for intervention (Grandner and Drummond, 2007; Patel et al., 2012, 2006).

There are a number of limitations that should be considered when interpreting the present findings. First, the sleep measures were assessed via self-report and thus subject to recall bias. In this regard, prior work employing both sleep diaries and polysomnography demonstrates that self-reported short sleepers underestimate how much sleep they truly obtain while long sleepers overestimate their sleep duration (Patel et al., 2009). Relatedly, self-

Table 4
Mean levels of inflammation and (standard errors) across sleep duration groups.

	Normal sleepers[b] (7–9 h)	Short sleepers (≤6 h)	Cohen's *d*	*p*-value	Long sleepers (≥10 h)	Cohen's *d*	*p*-value
CRP mg/L[a]							
Model 1	1.25 (1.03)	1.22 (1.04)	0.025	0.575	1.72 (1.12)	0.283	0.005
Model 2	1.26 (1.03)	1.20 (1.04)	0.039	0.387	1.68 (1.12)	0.260	0.011
Model 3	1.26 (1.03)	1.21 (1.04)	0.033	0.462	1.65 (1.12)	0.240	0.018
Interleukin-6 pg/ml[a]							
Model 1	0.75 (1.02)	0.75 (1.04)	0.005	0.916	1.08 (1.10)	0.392	<0.001
Model 2	0.75 (1.02)	0.74 (1.04)	0.009	0.841	1.05 (1.10)	0.356	<0.001
Model 3	0.75 (1.02)	0.75 (1.04)	0.009	0.837	1.04 (1.10)	0.342	0.001
TNF-α pg/ml[a]							
Model 1	0.83 (1.02)	0.83 (1.02)	0.011	0.809	0.91 (1.06)	0.154	0.126
Model 2	0.83 (1.02)	0.83 (1.02)	0.000	0.981	0.90 (1.06)	0.129	0.200
Model 3	0.83 (1.02)	0.82 (1.02)	0.003	0.961	0.90 (1.06)	0.118	0.186

Model 1: adjusted for age, gender, education, and body mass index; Model 2: Additionally adjusted for health indicators (smoking status, alcohol use, presence of cardiovascular disease and diabetes, number of medical conditions, statin use, anti-inflammatory medication use); Model 3: Additionally adjusted for psychotropic medication (benzodiazepines and anti-depressant use) and psychiatric diagnostic status.
[a] To normalize distributions CRP, IL-6, and TNF-α values were natural log transformed; for interpretation purposes means are presented as back-transformed.
[b] Reference group in sleep duration analyses.

reported long sleep duration may reflect extended time in bed rather than actual sleep (Patel et al., 2012). Future studies employing polysomnography are needed to address this possibility. In addition, the sleep duration measure employed required categorical responses, limiting variability. Second, approximately 14.4% of the sample was excluded from the present analyses. This study cannot account for the possibility certain characteristics were systematically missing that could affect these findings. Among other things, the excluded participants were more likely to be on antidepressants and had higher rates of comorbid depression and anxiety compared to those included in this analysis. These differences may reflect more severe psychiatric illness among those excluded, which may have led to an underestimation of the influence psychiatric status had on the sleep-inflammation association. Third, it is unclear whether the sleep measures estimate a state or trait characteristics. For example, while the measure of sleep duration estimated sleep over the past month it is possible that this self-report could coincide with a current major depressive episode in some participants but not in others, thus making it difficult to disentangle sleep disturbance as a symptom from sleep disturbance as correlate. Additional longitudinal analyses tracking the development of sleep changes in the context of psychopathology is warranted. Fourth, this study did not explicitly assess for sleep disorder, such as hypersomnolence or obstructive sleep apnea (OSA), the latter of which has previously been linked to heightened inflammatory activity. While we statistically adjusted for other known OSA correlates, including body mass index and presence of cardiovascular disease, this does not fully address the varied contributions OSA could have on inflammation and sleep. That said, prior research has documented a link between long sleep duration and inflammation, independent of diagnosed OSA (Patel et al., 2009). Nevertheless, future studies employing objective measures of sleep and sleep disorders, including assessment of apnea risk are needed.

There are also several important strengths to this study, such as a large sample size, measurement of several inflammatory markers, and objectively defined clinical diagnoses of depressive and anxiety disorders. The NESDA sample is well characterized on psychopathology. While rates of comorbidity of depression and anxiety (23.6% of the sample) may appear high in this sample, these rates are consistent with other epidemiologic samples (de Graaf et al., 2003; Jacobi et al., 2004; Kessler et al., 1994). In addition, rates of insomnia (as measured by the IRS), while high, are similar to those described elsewhere (Franzen and Buysse, 2008). Finally, given the complexity of the constructs addressed in the present analysis, the sample size allowed for statistical adjustment for a number of possible confounders.

In conclusion, this study extends the existing literature by supporting a link between long sleep duration and elevated levels of inflammatory markers (IL-6 and CRP) in a sample of persons with and without depressive and anxiety disorders. Additional prospective research investigating the etiology and biological consequences of long sleep duration is warranted.

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Contributors

Dr. Penninx designed the overall study and coordinated all data collection. Dr. Vogelzangs assisted in coordinating data collection. Dr. Prather wrote the first draft of the manuscript and carried out all statistical analyses. Drs. Penninx and Vogelzangs aided in editing the initial draft. All authors contributed to and approved the final manuscript.

Conflict of interest

The authors have indicated no financial conflicts of interest with respect to this manuscript.

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